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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Walke *et al.*	Group Art Unit: 1646
Application No.:	09/783,669	Examiner: O. Chernyshev
Filed:	02/14/01	
Title:	Novel Human 7TM Proteins and Polynucleotides Encoding the Same	Att Docket No.:LEX-0135-USA

AMENDMENT; AND RESPONSE TO FINAL OFFICE ACTION DATED DECEMBER 4, 2002

Commissioner for Patents
Alexandria, VA 22313

Sir:

The Applicants acknowledge the receipt of the Final Office Action ("the Action") mailed on December 4, 2002 (Paper No. 12), which has been carefully reviewed and studied. The Examiner is respectfully requested to enter the following amendments. Reexamination and reconsideration of the application is requested in view of the following amendments and remarks. In order to facilitate the Examiner's evaluation of the application, Applicants have attempted to address the rejections in Paper No. 12 in the same order in which they were originally raised.

A Petition for an Extension of Time of two months to and including May 4, 2003, which falls on a Saturday, and is therefore extended until May 5, 2003 under 37 C.F.R. § 1.7, and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(3) from Applicants' Deposit Account are included. The response is thus timely filed. Applicants believe no fees in addition to the fee for the extension of time are due in connection with this response. However, the Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-0892.

RESPONSE

I. Status of the Claims

Claims 1-7 are presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**.

II. Rejection of Claims Under 35 U.S.C. § 101

The Action continues to reject claims 1-7 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility. Applicants respectfully traverse.

The Action disagrees, that Applicants assertion based on the evidence that essentially the same protein was identified by those of skill in the art in no way associated with Applicant indicates that Applicants assertions are credible. Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible."

In the previous response (Paper No. 7) Applicants submitted clear evidence that those of skill in the art would recognize the sequences of the present invention as variants of a G protein- coupled receptor (GPCR), more specifically MRGX2, a GPCR that is expressed in sensory neurons that function to detect painful stimuli. Therefore, clearly, there can be no question that Applicants' asserted utility for the described sequences is "credible." Applicants have thus supplied evidence supporting their assertion that those of skill in the art would recognize that the sequences of the present invention encode a G protein-coupled receptor, in particular that of MRGX2.

A novel GPCR present in sensory neurons that function to detect painful stimuli would be readily recognized by those of skill in the art as having particular utility for its biological role and as a drug target. Both agonists and antagonists directed at this novel GPCR would have a clear utility in the management of the pain associated with, *inter alia*, surgery and cancers. Applicant's assertion also supports a "well-established" utility in that a person of ordinary skill in the art would immediately

appreciate why the invention is useful based on its identity as a GPCR, a well known family of proteins with well established ,specific and substantial utility. Clearly, there can be no question that Applicants' asserted utility for the described sequences is "credible." Applicants have thus supplied evidence supporting their assertion that those of skill in the art would recognize that the sequences of the present invention encode a G protein-coupled receptor, in particular variants of human MRGX2 receptor. Applicant's assertion also supports a "well-established" utility in that a person of ordinary skill in the art would immediately appreciate why the invention is useful based on its identity as a GPCR, a well known family of proteins with well established ,specific and substantial utility.

In contrast, the Examiner has provided additional articles that allegedly argue against the value of structure-function relationships. The Action (on page 4, lines 13-14) asserts that based on the introduction to a 17 year old article that "one cannot assume *a priori* that such change will not significantly alter the properties of a protein". First, Applicants note that the state of the art, and the reliability of its methodologies have progressed significantly in the 17 years since this article was published. Second, Applicants believe that those of skill in the art would readily recognize that one cannot assume *a priori* that such a change would significantly alter the properties of a protein either, as many amino acid substitutions do not effect function, particularly when like amino acids are involved.

In an article clearly labeled as an editorial overview, Bork and Eisenberg (Current Opinion in Structural Biology, 1998, 8:331-332) introduce nine reviews that "chart new methods for understanding the biological messages of genome sequences. Thus, clearly, whatever else Bork and Eisenberg believe, they recognize that sequences contain biological messages. Bork's later publications, for example, Genome Research *10*:398-400, 2000, in which analysis of prediction accuracy are presented, the reported accuracy of the methods which Applicants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, "Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Applicants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's

intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement. All of the issues raised in these articles can effect the accuracy of sequence base analysis, however all can be overcome by a more careful analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm are a staring point for consideration, and one of skill in the art can then through further analysis, structure - function analysis, etc., can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1B.S. and 2 Ph.D. level scientists). Clearly such highly skilled and careful analysis reduces the influence of such issues.

In summary, a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1 B.S. and 2 Ph.D. level scientists).

The present nucleotide sequences clearly encode a novel human GPCR, as detailed throughout the specification. The specification also teaches that GPCRs are associated with a wide variety of cellular functions, and as such, that GPCR interacting proteins have been subject to intense scrutiny as potential drug targets. Applicants have provided evidence that their assertions were credible and that the sequences of the present invention have utility. Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips.

However, the Action also discounts Applicants' assertion that the sequences of the present invention have utility in tissue specific expression analysis, such as that performed using DNA chips.

In spite of the fact that such tissue specific gene expression analysis is the basis of an entire industry, of which Affymetrix is perhaps the most noted company. The "real world" substantial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of such gene sequence data.

The Final Action discounts Applicants' assertion regarding the use of the presently claimed polynucleotides, as on DNA chips, based on the position that such a use would allegedly be generic. Further, the Action seems to be requiring Applicants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence **is not required** to track expression patterns using a DNA chip. As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The claimed sequence provides a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details at least on page 9.

Additionally, the Examiner inexplicably equates the value of the sequences of the present invention to that of a purified compound used to calibrate instruments or assays. The sequences of the present invention are the result of a complex biological process. Only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Not all human genomic DNA sequences encode proteins. The sequences of the present invention provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the

practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Such information clearly has more value than purified compound used to calibrate instruments or assays and argues against the Examiner's position that such uses are "generic".

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit B**. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by more than 1 exon spread non-contiguously along a region of human chromosome 11, which are contained within clone, AC027026.10. Thus clearly one would not simply be able to identify the more than 1 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were.

Finally, the Examiner has determined that applicants argument of due process presented in previous response is not persuasive. Applicants understanding is that issued United States patents retain a legal presumption of validity which in this case indicates that the inventions claimed in the cited patents are *legally presumed* to be in full compliance with the provisions of 35 U.S.C. sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not

have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. That is what the Applicants are respectfully requesting the Examiner to consider in the present matter. As the issued U.S. Patents cited above are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph, Applicants respectfully submit that the presently claimed polynucleotide must also meet the requirements of 35 U.S.C. § 101.

For each of the foregoing reasons, Applicants submit that in light of the above discussion and those presented in previous Applicant responses, the presently claimed invention has been shown to have a substantial, specific, credible and well-established utility and that the rejection of pending claims 2, 3, 6 and 7 under 35 U.S.C. § 101 has been avoided, and respectfully request that the rejection be withdrawn.

III. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 1-7 are also rejected under 35 U.S.C. § 112 first paragraph. Specifically, since the claimed invention is not supported by either specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation, as set forth previously. Applicants submit that, as the present invention has been demonstrated in the previous section to have specific, substantial and well established utility that this rejection has been overcome.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Chernyshev have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

May 5, 2003

Date

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